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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/072,621	REINER ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 27 January 2004.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-5,8-12,14,15 and 20-32 is/are pending in the application.

4a) Of the above claim(s) 21-32 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5,8-12,14,15 and 20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-5,8-12,14,15 and 20-32 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 27 January 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Response and Amendment filed 27 January 2004 has been received and entered in full.

2. Newly submitted claims **21-32** are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 21-32 are drawn to method of identifying methods that decrease amyloid precursor protein expression or inhibit the activity of an ABC transporter. The originally elected claims require search and consideration of regulating expression of amyloid precursor protein in a cell while the new claims require search and consideration of screening methods. These searches are not co-extensive and thus present a search burden on the Examiner. These are outside the scope of the elected invention of decreasing expression of amyloid precursor protein in a cell via decreasing expression of an ABC transporter.

3. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims **21-32** are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP §821.03.

4. The newly submitted subject matter in claims 2 and 9 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 2 and 9 are drawn to ABCB6, ABCG2, ABCA1, ABCA2, ABCA3, ABCA5, ABCA6, ABCA8, ABCA9, ABCC5, ABCC10, ABCD1, ABCD2, and ABCD4. These are species are outside the

scope of the elected invention of ABCB9, ABCG1, and ABCG4 pursuant to the previous Office Action (12 August 2003).

5. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the species ABCB6, ABCG2, ABCA1, ABCA2, ABCA3, ABCA5, ABCA6, ABCA8, ABCA9, ABCC5, ABCC10, ABCD1, ABCD2, and ABCD4 listed in claims **2** and **9** are withdrawn from consideration as being directed to a non-elected inventions. See 37 CFR 1.142(b) and MPEP §821.03.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

7. The Objection to claims **7** and **13** as set forth at pp. 2 ¶5 in the previous Office Action (12 August 2003) is hereby *withdrawn* in view of Applicant's cancellation of said claims (27 January 2004).

8. The Rejection of claims **1, 7, 8,** and **13** under 35 U.S.C. 112 2 as set forth at pp. 13 ¶36-37 in the previous Office Action (12 August 2003) is hereby *withdrawn* in view of Applicant's amendments (27 January 2004).

9. The Rejection of claims **1-12** under 35 U.S.C. 112 2 as set forth at pp. 13 ¶38 in the previous Office Action (12 August 2003) is hereby *withdrawn* in view of Applicant's amendments (27 January 2004).

Maintained Objections And/Or Rejections

10. Claims **2** and **9** are objected to because of the following informalities: said claims recited non-elected species of ABC (ABCB6, ABCG2, ABCA1, ABCA2, ABCA3, ABCA5, ABCA6, ABCA8, ABCA9, ABCC5, ABCC10, ABCD1, ABCD2, and ABCD4). Appropriate correction is required.

11. Claims **1-5, 8-12, 14-15,** and **20** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons as set forth at pp. 3-11 ¶6-29 in the previous Office Action (12 August 2003).

12. Applicant traverses this rejection on the following grounds: **(a)** the Specification as filed provides sufficient guidance for methods of decreasing expression of APP (amyloid precursor protein) in a cell comprising contacting said cell with a small molecule that decreases expression or inhibits activity of an ABC transporter, **(b)** the Specification contains prophetic examples and uses ABC mutants (Walker A or Walker B motifs), **(c)** amyloid-β (also known as β-amyloid) and amyloid precursor protein are not identical and the present claims relate to a method for decreasing the expression of amyloid precursor protein and not to a method for decreasing amyloid-β expression, **(d)** cell-based methods are predicable, useful, and accepted in the art for analyzing agents and method effective for treating conditions and disease related to amyloidosis such as Alzheimer's disease, **(e)** the instant Specification enables a person skilled in the art to practice the claimed methods using ABC transporters that are expressed in a brain cell, **(f)** ABC

transporters are present in neuronal tissues and are capable of affecting amyloid precursor protein expression, and **(g)** Applicant has stated that: "These compounds include a small molecule, which may be identified readily and without undue extermination by using routine screening methods." (pp. 14-15 Response filed 27 January 2004), Applicant then details suggestions for experiments to identify, make, and use said small molecule (compound) (pp. 15-16).

13. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons:

14. On "**(a)**", as a whole the instant claims are an invitation to experiment. While small molecules which decrease expression or inhibit activity of an ABC transporter may constitute a fecund ground for investigation, the CAFC ruled in *Genentech Inc. v. Novo Nordisk A/S* (CA FC) **42 USPQ2d 1001** (1997) that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Citing *Brenner v. Manson,* **383 U.S. 519, 536, 148 USPQ 689, 696** (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Therefore the CFAC stated that tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. That requirement has not been met in the instant specification with respect to the any small molecules which decrease expression or inhibit activity of an ABC transporter which in turn decreases APP expression.

15. On "**(b)**", all of the Specifications examples are either suggestions or directed to examples (ABC mutants) other than small molecules that decrease expression or inhibit activity of an ABC transporter. Therefore, no guidance is present to adequately address the undertaking of the invention as claimed.

16. On "**(c)**", the Examiner notes that both independent claims under consideration, 1 and 8 both clearly state "*...decreases expression of amyloid precursor protein in the cell.*" in the last line of each claim. Since β-amyloid is a proteolytic product from amyloid precursor protein, the two are inexorably connected. This is reiterated by the Applicant but does not offer any support to the regulation of expression of APP via decreasing ABC expression. Because Lam *et al.* (February 2001) "β-Amyloid efflux mediated by p-glycoprotein." Journal of Neurochemistry **76**(4): 1121-1128 teaches that p-glycoprotein (p-gp), a member of the ABC transporter family, is an $A\beta_{1-40}$ and $A\beta_{1-42}$ transporter (Figure 3). Further, Lam *et al.* teaches that inhibition of p-gp with RU486 and RU49953 reduces Aβ secretion (Figure 2). It is noted that this satisfies a limitation of claim 8, wherein the activity of an ABC transporter is regulated, as inhibition is a form of regulation. However, the expression of Aβ was not affected *per se*, but the secretion (pp. 1127). This evidence is to the nature of the claims because Aβ secretion is regulated, as a reduction is a form of regulation, but not expression. Therefore art concerning β-amyloid processing is critical to understanding the undertaking of the instant invention.

17. On "**(d)**", the question of whether or not cell-based methods are useful has not been raised. The issue at hand is whether or not the large quantity of experimentation necessary to identify all the applicable small molecules that may or may not decrease expression or inhibit activity of an ABC transporter, the lack of direction/guidance presented in the specification

regarding synthesizing, screening, and evaluating all applicable small molecules that may or may not decrease expression or inhibit activity of an ABC transporter, the absence of working examples directed to known small molecules that may or may not decrease expression or inhibit activity of an ABC transporter, the complex nature of the invention, the unpredictability of the effects of small molecules that may or may not decrease expression or inhibit activity of an ABC transporter on cells and/or patients, and the breadth of the claims which fail to recite limitations for what constitutes an applicable small molecules that may or may not decrease expression or inhibit activity of an ABC transporter, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

18. On "**(e)**", Schmitz *et al.* (2001) "Role of ABCG1 and other ABCG family members in lipid metabolism." Journal of Lipid Research **42**: 1513-1520 teaches that ABCG1 and ABCG4 are widely expressed but does not detail that they have been found in the nervous system, specifically the brain. Further, other ABCG family members are concentrated in the small intestine and liver. Thus the breath of the claims is not supported by the expression pattern of ABCG family members. However, Applicant reiterates the assertion that the invention is enabled but has not detailed in what manner the obstacles may be overcome or what critical steps must be taken to undertake the invention.

19. On "**(f)**", the question of whether or not ABC transporters exist in neuronal tissue has not been raised. The issue at hand is whether or not the large quantity of experimentation necessary to identify all the applicable small molecules that may or may not decrease expression or inhibit activity of an ABC transporter, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable small molecules that may or may

not decrease expression or inhibit activity of an ABC transporter, the absence of working examples directed to known small molecules that may or may not decrease expression or inhibit activity of an ABC transporter, the complex nature of the invention, the unpredictability of the effects of small molecules that may or may not decrease expression or inhibit activity of an ABC transporter on cells and/or patients, and the breadth of the claims which fail to recite limitations for what constitutes an applicable small molecules that may or may not decrease expression or inhibit activity of an ABC transporter, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

20. On "**(g)**", Applicant has admitted on the record that inventors are not in material possession of the "small molecule" in question but have disclosed a vast number of possible candidates from which the desired molecule may or may not be isolated.

21. On "**(h)**", as stated above, Applicant's statement is interpreted as an invitation to experiment. While small molecules which decrease expression or inhibit activity of an ABC transporter may constitute a fecund ground for investigation, the CAFC ruled in *Genentech Inc. v. Novo Nordisk A/S* (CA FC) **42 USPQ2d 1001** (1997) that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Citing *Brenner v. Manson,* **383 U.S. 519, 536, 148 USPQ 689, 696** (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Therefore the CFAC stated that tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members

of the public to understand and carry out the invention. That requirement has not been met in the instant specification with respect to the any small molecules which decrease expression or inhibit activity of an ABC transporter which in turn decreases APP expression.

22. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known amyloid precursor protein (APP) expression regulators to correlate with ABC transporter activity. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

23. Claims **1-5, 8-12, 14-15,** and **20** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons as set forth at pp. 11-13 ¶30-35 in the previous Office Action (12 August 2003).

24. Applicant traverses this rejection on the following grounds: **(a)** Applicants possess the claimed invention, **(b)** the Specification describes the relationship between the level of expression of an ABC transporter and the level of amyloid precursor protein in a cell, and **(c)** small molecules that decrease amyloid precursor protein expression may be readily obtained from any one of a number of combinatorial libraries.

25. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons:

26. Claim 1 requires a "small molecule" that can decrease the expression of an ABC transporter. Claim 8 requires "small molecule" that can inhibit the activity of an ABC transporter.

27. However, the claims do not require that the small molecule to possess any particular conserved structure, or other distinguishing feature. Thus, the claims are drawn to a genus of agents that is defined by desired activity. Furthermore the art recognizes that "small molecule" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds.

28. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of desired activity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

29. Applicant has stated that: "Small molecules that decrease amyloid precursor protein expression may be readily obtained from any one of a number of combinatorial libraries." (pp. 17 Response filed 27 January 2004) and "These compounds include a small molecule, which may be identified readily and without undue extermination by using routine screening methods." (pp. 14-15 Response filed 27 January 2004). Applicant has admitted on the record that inventors are not in material possession of the "small molecule" in question but have disclosed a vast number of possible candidates from which the desired molecule may or may not be isolated.

30. But to satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

31. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co. et al.* CAFC [(03-1304) 13 February 2004]. In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting

prostaglandin synthesis in human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since the patent described the compound's desired function of reducing activity of the enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

32. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Summary

33. No claims are allowed.

34. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

35. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
April 9, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER